

CHEMICAL PROTECTION AGAINST IONIZING RADIATION

ZÉNON M. BACQ

Professor at the University of Liège (Belgium)
Member, Académie Royale, Classe des Sciences
Member, Académie Royale de Médecine de Belgique
Foreign Member, Academy of Sciences U.S.S.R.

With an Introduction by SHIELDS WARREN,
M.D., Cancer Research Institute, New England
Deaconess Hospital, Boston, Massachusetts.

The phenomenon of chemical protection of mammals against ionizing radiation--discovered in 1949--attracted immediately the attention of scientists interested in the modes of action of radiation, in radiotherapy, or in health physics.

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By

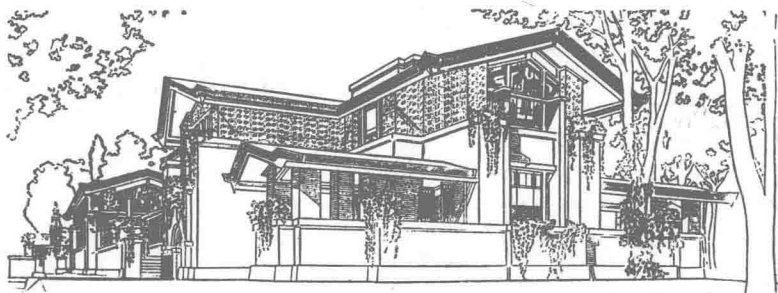
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SHIELDS WARREN, M.D.

*Cancer Research Institute
New England Deaconess Hospital
Boston, Massachusetts*



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CHEMICAL PROTECTION AGAINST IONIZING RADIATION

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AMERICAN LECTURE SERIES®

A Monograph in
The BANNERSTONE DIVISION of
AMERICAN LECTURES IN LIVING CHEMISTRY

Edited by
I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D.
Consultant of the Departments of Health and Hospitals
New York, New York

FOREWORD

Our Living Chemistry Series was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Bacq of Liège, Belgium, presents the current status of chemical protection against ionizing radiation in mechanism and management from experimental and clinical data with due regard to the specific implications of radiotherapy. The initial chemical changes induced by ionizing radiation proceed from metabolic derangements to cellular damage to cell destruction within days or weeks. Temporary ionization of intracellular water and constituents proceeds rapidly to irreversible alteration of nucleoprotein templates for enzymes and damage of the biochemical templates of the germplasm. The hazards involve biological effects on the world population for a period of time in the future comparable in length to the recorded history of the past.

The 1949 discovery of radioprotective substances led to the concept of chemical protection of mammals, demonstrable when the agent present in the organism during exposure, reduces the immediate biochemical lesions. This newer knowledge brings fresh awareness of the clinical urgency of radioprotection. It is the meeting point between ourselves on the one hand and the forces we can observe and study on the other. Man always protects himself from new discoveries for progress goes hand in hand with danger. These great problems of life and radiation will yield only to those whose knowledge of radiation suffuses their knowledge of life, whose knowledge of life quickens their knowledge of radiation. Chemical creativity will become the poetry of the medical mind.

*"Physician of the Future, what shall be
The Life of Earth that you shall see?
What strange new facts the years will show?
What wonders rare your eyes shall know?
To what new realms of marvel, say
Will conquering science war its way?"*

I. NEWTON KUGELMASS, M.D., PH.D., Sc.D., *Editor*

INTRODUCTION

During the troubled years of our generation the Pandora's box opened by man's control of atomic energy has been partly converted into an Aladdin's lamp through the development of peaceful uses of it. Indeed, were it not for the ready availability of this new and almost unlimited source of energy, the world would be hard pressed to support its expanding population. The more dependent on atomic energy we become, the more ionizing radiation is utilized in medical advances, the more important protection against ionizing radiation becomes. Man has no choice but to learn to live with radiation. An important factor in this will be the development of means of chemical protection against it.

Dr. Bacq in this monograph has brought together in creative yet critical fashion the pertinent data concerned with the chemical protection of warm-blooded animals and man. Dr. Bacq through his own research in this field has made major contributions. His position as past Chairman of the United Nations Scientific Committee on the Effects of Atomic Radiation acquainted him also with the broad implications of the field. In addition, Dr. Bacq's experience as a pharmacologist has led him to a broad experimental pathway, reinforcing the earliest protective measures and using warm-blooded animals as test objects. He pointed out early that peroxides produced by ionizing irradiation of water and watery solutions had some radiomimetic effects in addition to being products of radiation. He clearly demonstrated the protection afforded by cyanide in irradiated mice. This was followed by establishment of the fact that protection by various substances was effective before and not after radiation.

Dr. Bacq brings together the data in this important field and summarizes particularly the role of SH- and NH₂-containing substances. His guidance is particularly helpful because of his present

participation in the complex and at times frustrating developments in this line of research. A very useful though minor feature of the monograph is the provision of a standard nomenclature for useful substances. The historical introduction is well done, but the author's own contributions are perhaps less emphasized than would be the case of a more detached author. Dr. Bacq points out in passing that about 10 per cent of the time and publications of congresses, meetings, and periodicals devoted to radiation research are concerned with radiation protection.

A general summary of the protective compounds is of great value, particularly to the neophyte in the field. The chapter on pharmacology is particularly helpful, as the data until now have been scattered in a great diversity of publications. An added value of this chapter is a presentation of some of the other effects than radiation protection as encountered in the radioprotective substances. Related to this is a very adequate discussion of the metabolic problems that may be induced by the use of protective chemicals. He includes also useful summarizations of the experiments dealing with the reactions of intracellular structures such as mitochondria to ionizing radiation and the role of protective substances in relation to them. The student of this field cannot do without this scholarly study which makes readily available and more comprehensible the complex and sometimes contradictory findings.

SHIELDS WARREN, M.D.

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**CHEMICAL PROTECTION AGAINST
IONIZING RADIATION**

I DEFINITION AND SCOPE

Chemical protectors (or radioprotectors) are substances which, administered to an animal or added to a culture medium shortly before exposure to ionizing radiation decreases significantly the effects of this radiation; administration after irradiation is without favourable effect.

Certain substances are known to be slightly effective when given either before or after irradiation; such is the case of olive oil (Maqsood and Ashikawa, 1960; Maqsood, 1962), of parathyroid hormone (Rixon *et al.*, 1958), of diisopropylfluorophosphate (Willoughby, 1961), of nicotinamide (Myers *et al.*, 1962), of lycopene (Forssberg *et al.*, 1960). They cannot be considered as true protectors. All the manipulations of animals or other living material after irradiation must be considered as therapeutic measures which enhance the process of recovery or replace dead cells. Such is the case with bone-marrow transplantation, certain spleen extracts (Ellinger *et al.*, 1962; Katz and Ellinger, 1963), alkoxyglycerols (Brohult, 1962), various phosphate esters of adenosine (ATP, AMP, etc.) and pyridoxal-5-phosphate (Melching, 1963), injections of olive oil (Ashikawa and Anderson, 1960), of nucleic acids (see for instance Pantić *et al.*, 1962) and, in bacteria, chloramphenicol (Herčík, 1960).

Sodium citrate and sodium chloride above a certain concentration ($\frac{1}{8}$ molar) in the medium decrease the amount of DNA leaking from a microorganism *Escherichia freundii* after irradiation (Osterrieth, 1962, 1963 a, b); this is a pure physical osmotic effect; it has been also observed with yeast, with other salts and with sugars.

Similarly, the drastic treatments of bacterial spores (mainly with various gasses at high pressure) which Powers (1961) uses

before and after irradiation in order to alter the primary chemical lesions inflicted by ionizing radiation, are not fully discussed here because the purpose of these experiments is different from our main aim.

Such terms as "post-irradiation protection" or "preprotection" should be excluded from the literature because they are misleading. The author, together with other radiobiologists (see Latarjet and Gray, 1964) has often insisted on the necessity of a logical and clear terminology.

We shall not restrict ourselves to mammals, as some have done (Thomson, 1962, for instance) because it is clear that chemical protection must be discussed at three levels: a) in chemical systems; b) at the cellular level; c) in mammals (or complex organisms) (see *Radiation Effects in Physics, Chemistry and Biology*, 2d Intern. Congress of Radiation Research, Harrogate, 1962; North Holland Publishing Comp., Amsterdam, 1963). Chemical protection is a biological and physico-chemical phenomenon which cannot be understood unless all the evidence from dry synthetic polymer to mammals is put together. The part played by the microbiologists cannot be neglected; many experiments impossible to conduct in mammals are very easily done with spores, bacteria, yeast, phages or plant material. Is it not true that one of the leading ideas of contemporary biochemistry is the *unity in chemical processes* as well as in fundamental structure of all living matter?

★ ★ ★

There are good reasons to link chemical and physical protection with the natural recovery processes which are inherent to every cell or organism. They have been explained many times by A. Hollaender (see for instance, *Radiation Protection and Recovery*, Pergamon Press, 1960). There are two oxygen effects: O_2 during irradiation increases damage, but without O_2 after irradiation, restoration cannot occur. If the author has taken the decision not to discuss restoration, it is because chemical protection, *sensu stricto* has become a very complicated subject in recent years, and because a guide written by somebody who has actively